Targeting *ErbB2* aberrations in non-small cell lung cancer

Xuan Ge[1], Sara Tariq[2], Haiying Cheng[2], Balazs Halmos[2]

[1]Department of Internal Medicine, Jacobi Medical Center, Bronx, New York, USA; [2]Department of Medical Oncology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA

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Correspondence to: Balazs Halmos, MD. Department of Medical Oncology, Montefiore Medical Center, Bronx, New York, USA.
Email: bahalmos@montefiore.org.

Abstract: Human epidermal growth factor 2 (*HER2* or *ErbB2*) mutations in lung cancer are oncogenic drivers similar to epidermal growth factor receptor (*EGFR*) mutations in non-small cell lung cancers. Until recently, *ErbB2*-mutant lung cancers have generally been resistant to various targeted agents. However, a new wave of *ErbB2*-targeting drugs has shown promise for this subset. We highlight a case of a patient with an *ErbB2*-mutant lung cancer with an exon 20 YVMA insertion who had a good response to poziotinib and review the current literature on the methods of testing for *ErbB2* mutations and the efficacy of various known and emerging targeted agents.

Keywords: *ErbB2* mutations; exon 20 YVMA insertion; poziotinib; non-small cell lung cancer (NSCLC)

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Introduction

Human epidermal growth factor 2 (HER2 or ErbB2) is a receptor tyrosine kinase of the ERBB family, which also includes EGFR, HER3 and HER4. These receptors each contain an extracellular ligand binding region, a hydrophobic transmembrane domain as well as an intracellular domain with tyrosine kinase catalytic activity. When ligands bind to the extracellular domains of EGFR, HER3 and HER4, these receptors form heterodimers, which in turn activate various signaling cascades including the raf/mitogen-activated protein kinase (MAPK), phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), and protein kinase C (PKC) pathways. These pathways play essential roles in cell proliferation, differentiation, angiogenesis and protection from apoptosis. Interestingly, although it is structurally quite similar to its relatives, there are no identified ErbB2-specific ligands. Instead, ErbB2 is constitutively activated, serves as the preferred dimerization partner for the other receptor kinases and heterodimers containing ErbB2 are rather stable and potent (1). As a result, deregulation and overexpression of *ErbB2* leads to increased formation of these heterodimers, which in turn activate signaling cascades that potentiate cell proliferation, and ultimately serves as a potent driver of oncogenesis. Therefore, two main strategies have emerged in targeting *ErbB2* amplification and mutations: antibodies (and antibody-drug conjugates), which are directed at the extracellular domain, and tyrosine kinase inhibitors (TKIs), which target the intracellular kinase domain. Especially promising among these is poziotinib, a novel, quinazoline-based irreversible TKI, which has shown efficacy in patients with exon 20 mutations.

Case presentation

A 68-year-old gentleman with a remote smoking history and no significant medical comorbidities presented initially with a persistent cough that had worsened over the course of several months. A chest computed tomography (CT) showed a right upper lobe mass with associated adenopathy, and a positron emission tomography (PET)/CT demonstrated PET-avid liver, adrenal and bony metastases. He was referred for a CT-guided biopsy of the right iliac bone, and

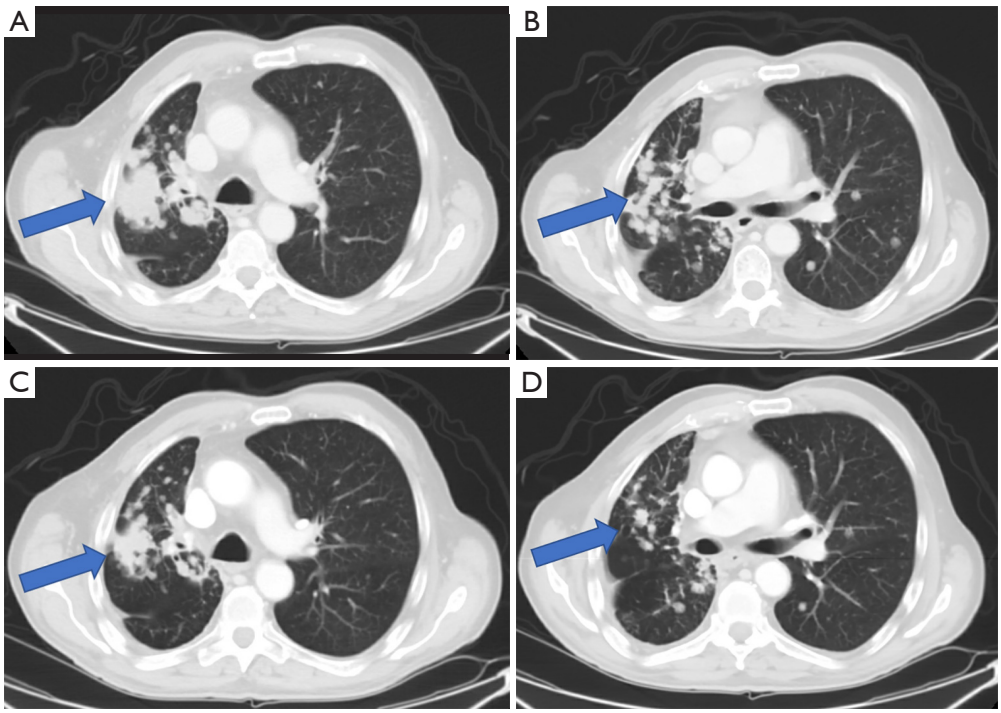

Figure 1 Imaging prior to (A and B) and after (C and D) treatment with poziotinib shows significant reduction in burden of disease. The blue arrows highlight these changes.

results showed a TTF1^{+} adenocarcinoma compatible with lung origin. Unfortunately, the specimen was not sufficient for further molecular testing. Further workup included a brain magnetic resonance imaging (MRI), which showed multiple small (less than 4 mm) lesions, consistent with brain metastases, and a repeat bone biopsy, which ruled out the presence of EGFR/ALK abnormalities and showed advanced, *ErbB2* YVMA mutated lung adenocarcinoma. The patient received stereotactic radiosurgery (SRS) for the brain metastases, and a repeat brain MRI showed resolution of all but one lesion, which showed treatment-related changes. He was started on treatment with carboplatin/pemetrexed/pembrolizumab and initially had an excellent response. However, after approximately 8–9 months of treatment, he was found to have bony progression in the left hemipelvis. Extended molecular testing at that time confirmed the above *ErbB2* mutation. He was then given second-line treatment with docetaxel/ramucirumab. The patient developed considerable adverse effects related to this regimen after just 2–3 cycles and was subsequently started on the anti-ErbB2 drug conjugate, ado-trastuzumab emtansine (T-DM1) at an outside institution. However, within several months, he was found to have progression in central nervous system (CNS) metastases and received whole brain radiation therapy. He then resumed care at our institution and was started on poziotinib 16mg daily on a research protocol. After just one cycle of treatment, imaging showed improvement with significant reduction in burden of metastatic disease (*Figure 1*). Unfortunately, later significant toxicities developed preventing patient from being able to continue study medicine with subsequent decline in performance status.

Molecular tumor board

Oncogenic activation of *ErbB2* occurs primarily by three mechanisms: amplification and overexpression, somatic mutations of the receptor and inhibition of phosphatase activity (2). *ErbB2* amplification was first discovered in breast cancer and is found in 15–30% of invasive breast carcinomas. In that setting, it serves both prognostic and predictive value as it is associated with shorter progression-free and overall survival (3). *ErbB2* amplification has now been identified in various other cancers as well, including ovarian, uterine, gastric, colon, bladder, lung and is a validated treatment target in gastric adenocarcinoma. More

recent studies have shown that deregulation of the *ErbB2* gene can also result from various somatic mutations. First identified in lung adenocarcinoma, these have now been identified in various other malignancies as well. As with *EGFR* mutations, which are mutually exclusive with *ErbB2* mutations, the latter have more commonly been identified in non-smokers, women, Asians and in adenocarcinoma (4). Activation of *ErbB2* can result from missense mutations or insertions in the kinase domain, as well as from missense mutations (such as the S310 single-site substitution) or deletions of the extracellular domain. The most common alterations of *ErbB2* involve in-frame insertions in exon 20, such as the YVMA insertion at codon 776. These mutations result in a conformational change in the autoinhibitory αC-β4 loop, which narrows the ATP-binding site and as a result promotes constitutive kinase activity (5). Less common are missense mutations in the extracellular domain. These promote constitutive kinase activity by either inducing disulfide bond formation (such as S335C or G309E) or by increasing C-terminal tail phosphorylation (such as S3105 and S310Y) (6). Lastly, *ErbB2* can be activated by inhibition of phosphatase activity, and this is supported by *in vitro* studies which have shown that inactivation of the PTPN12 phosphatase promotes *ErbB2* activation (7).

ErbB2 alterations can be identified using various diagnostic assays including enzyme-linked immunosorbent assay (ELISA), immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), as well as next generation sequencing (NGS) (4,8,9). However, no gold standard exists. Traditionally, the most commonly used methods to detect ErbB2 amplifications have been IHC, to quantify the ErbB2 protein as well as FISH to determine the *ErbB2* gene copy number. While the former is widely available and easy to perform, results are variable and depend on a variety of factors including the antibody used as well the cutoffs used to define positivity. FISH, on the other hand, is not as easily available but much more specific. As a result, in breast cancer, IHC is often used a screening test, and a reflex FISH is performed if results are equivocal. In non-small cell lung cancer (NSCLC), however, this approach has not been favored as there is often significant discordance between IHC and FISH results (10). More recently, dual in situ hybridization (DISH) has been shown to be better at detection of *ErbB2* amplification compared to FISH (11). *ErbB2* mutations, on the other hand, can be detected using Sanger sequencing, NGS as well as mass spectrometry genotyping. Of these, NGS is highly sensitive, and allows for the detection of various mutations, rearrangements as well as amplifications, and is the preferred methodology for molecular testing in lung cancer as it can detect all potential actionable alterations.

Patients with *ErbB2* aberrations have a shorter overall survival than those with other oncogenic drivers (12), and there remains a significant unmet need to develop the optimal targeted therapy for these patients. At present, two main strategies have been used in targeting *ErbB2* amplification and mutations: antibodies (and antibody-drug conjugates), which are directed at the extracellular domain, and TKIs, which target the intracellular kinase domain (2).

Trastuzumab, a humanized monoclonal antibody that targets the extracellular domain of the *ErbB2* receptor, is standard of care in the management of *ErbB2*-amplified breast cancer. Unfortunately, early studies did not show similar efficacy or survival benefit in NSCLC as a single agent (13) or when combined with gemcitabine-cisplatin (14) or docetaxel (15). However, it is important to note that these early trials selected patients on the basis of *ErbB2* positivity on IHC and we now know that *ErbB2* mutations, which do not always result in *ErbB2* overexpression, likely play a more important role in oncogenesis in NSCLC. More recent retrospective analyses have provided more promising results. A 2013 study identified 65 patients with *ErbB2* mutations, 16 of which were treated with trastuzumab-based therapies after conventional chemotherapy, and reported a disease control rate of 96% (16). A similar retrospective analysis of a cohort of 101 patients with *ErbB2* exon 20 mutations identified 65 patients who had received *ErbB2*-directed therapy after conventional chemotherapy. Of these, 57 patients had received trastuzumab in combination with chemotherapy, suggesting a disease control rate of 50%, and supporting the use of combined regimens (17). T-DM1, an *ErbB2*-targeted antibody-drug conjugate, has shown benefit as well. A study by Li *et al.* in 2018 showed a partial response rate of 44% and median progression-free survival (PFS) of 5 months in 18 patients with advanced, *ErbB2*-mutant lung adenocarcinomas who were treated with T-DM1 (18). These patients had various *ErbB2* mutations including exon 20 insertions and point mutations in the transmembrane and extracellular domains.

TKIs have been studied in this setting as well. Afatinib, an irreversible inhibitor of EGFR, ErbB2, and HER4, has shown some efficacy in case reports and retrospective reviews. In a series of three patients with various *ErbB2* exon 20 mutations, each achieved a partial response, lasting as long as 4 months (19). Another case report showed a more durable, 10-month response in a patient with the common exon 20

Table 1 Summary of efficacy/major AEs with agents/trials

Agents	Mechanism of action	Eligibility	Efficacy	AEs	Reference
T-DM1	Cytotoxic anti-microtubule agent released within the target cells upon degradation of the human HER2-T-DM1 complex in lysosomes	IHC 3+ Mutation Amplified/mutation	44% (partial response rate)	Fatigue, nausea, bone and joint pain, muscle pain, thrombocytopenia headache, constipation, nerve damage, anemia, hypo-potassium	(18)
Pertuzumab, trastuzumab	Humanized mAb directed against the extracellular domain of the tyrosine kinase receptor HER2	Amplified Mutation	50–96% (disease control rate)	Cardiac failure, cardiomyopathy, CHF, pulmonary infiltrates, anemia, neutropenia	(13-17)
Afatinib	Irreversibly binds to the intracellular tyrosine kinase domain, subsequently inhibits EGFR, HER2 and HER4 receptors	Mutation	15% (partial response rate)	Pulmonary toxicity, acute renal failure, hepatotoxicity, exfoliative dermatitis, hypokalemia	(19-21)
Dacomitinib	Irreversible binding at the ATP domain of the EGFR family kinase domains	Mutation Amplified	12% (partial response rate)	Interstitial lung disease, diarrhea, rash, hypokalemia	(22)
TAK788	EGFR antagonists; ERBB 2 receptor antagonists	Exon 20 mutation	20–56% (partial response rate)	Diarrhea, nausea, rash, vomiting, decreased appetite	(28,29)
Poziotinib	Inhibitor of *EGFR* and *HER2* exon 20 insertion mutants	Exon 20 mutation	50% (partial response rate)	Rash, diarrhea, paronychia	(30,31)

T-DM1, ado-trastuzumab emtansine; IHC, immunohistochemistry; HER2, human epidermal growth factor 2; AEs, adverse event; mAb, monoclonal antibody; CHF, congestive heart failure; EGFR, epidermal growth factor receptor.

YVMA insertion (20), and an international retrospective review of 27 patients with metastatic *ErbB2*-mutant disease showed a partial response rate of 15% (21). Dacomitinib, a second-generation, irreversible inhibitor of EGFR, ErbB2, and HER4, has been studied as well. A phase two trial enrolled 30 patients with *ErbB2* mutations or amplifications and found a partial response rate of 12% that lasted as long as 14 months in patients who had *ErbB2*-mutated disease. No partial responses occurred in those with *ErbB2* amplification or in those with the most common exon 20 insertion, A775_G776insYVMA (22). Neratinib, another second-generation TKI, produced a response rate of 19% and progression free survival of up to 18-plus months in a cohort of 43 patients with *ErbB2* mutations, when it was used in combination with the mammalian target of rapamycin (mTOR) inhibitor temsirolimus (23). Lapatinib, a dual TKI which inhibits ErbB1 and ErbB2, has been shown to be effective in *HER2*-positive breast cancer but has not demonstrated activity in NSCLC. More recently, preclinical data suggests that osimertinib may be effective in targeting *ErbB2* aberrations as well, particularly amplification (24). Tarloxotinib, a prodrug that releases an irreversible EGFR/ErbB2 TKI under hypoxic conditions, has also shown promising results in a recent *in vivo* study of murine xenografts of two adenocarcinoma cell lines with exon 20 mutations (25,26). After 4 weeks of treatment with tarloxotinib, the authors found significant reduction in tumor burden as compared to afatinib which did not alter tumor growth.

Although TKIs have certainly shown some activity, response rates are low and there are no approved agents for *ErbB2*-mutant lung cancer. Newer data is encouraging. TAK-788 (AP32788), an investigational TKI that targets *EGFR* and *ErbB2* mutations, is being studied in a phase I/II, open-label, multicenter study which administered the drug in dose escalation and expansion cohorts, which were based on tumor genotype. Initial data showed a partial response rate of 21% (n=14) in patients with *EGFR* exon 20 insertions (27) and more recently published data shows an objective response rate of 54% and disease control rate of 89% in the 26 patients assessed (28). The ongoing clinical trial will help assess efficacy in patients with *ErbB2* alterations (29). Equally exciting is data on poziotinib, a novel, quinazoline-based irreversible inhibitor of EGFR, ErB2 and HER4. This potent, small and flexible inhibitor is hypothesized to be more effective in those with exon 20 mutations as these alterations reduce the size of the drug-binding pocket, rendering most larger TKIs ineffective (30). A phase I/II trial of 50 patients with metastatic, *EGFR* or *ErbB2* exon 20-mutated lung adenocarcinoma showed an objective response rate of 50% and disease control rate of 83% in the latter group (31). The mean PFS for these patients was 5.1 months (*Table 1*). Further studies are

needed to determine the efficacy of these various agents.

Conclusions

Our patient showed an initial response to poziotinib reflecting the potential actionability of *ErbB2* mutations in non-small cell lung cancer, however further data is necessary to assess its effectiveness in patients with the YVMA exon 20 insertion. Our case highlights the importance of developing agents that precisely target the various *ErbB2* mutations, in particular the common YVMA exon 20 mutation, as these molecular alterations do not respond similarly to the various *ErbB2*-targeted agents.

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Footnote

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